EPA Harvard Center for Ambient Particle Health Effects: Exposure, Susceptibility, and Biological Mechanisms and Dosimetry

Progress Report for Second Year

Below we provide a brief progress report for the twelve projects included in our original Center proposal:

THEME I: ASSESSING PARTICLE EXPOSURES FOR HEALTH EFFECTS STUDIES

Project Ia: Assessing Human Exposures to Particulate and Gaseous Air Pollutants

We have performed a series of exposure studies in several cities located throughout the United States (Boston, MA, Baltimore, MD, Atlanta, GA, Los Angeles, CA, and Steubenville, OH). As part of these studies, we have collected several thousand simultaneous outdoor, indoor, and personal particle and gas samples for several potentially sensitive subgroups, including senior citizens, children, and individuals with chronic obstructive disease (COPD) or recent myocardial infractions (MI). For Atlanta and Steubenville, measurements of cardiovascular health status (heart rate, blood pressure, oxygen saturation, daily symptoms and medication use) were also collected for each participant. Data collection for the Steubenville and Atlanta studies were co-funded by the Center, while data collection for the remaining studies were supported by other agencies, such as HEI, EPRI, API and EPA (under a separate cooperative agreement).

As part of Project Ia, we have begun to analyze data from these studies to investigate (1) the contribution of particles of outdoor and indoor origin to personal PM2.5 exposures, (2) the potential for confounding by gaseous pollutants to affect epidemiological study results, and (3) the ability of particles to penetrate from outdoor to indoor environments. To date, we have published or submitted four papers addressing these issues (Sarnat et al., 2000; Sarnat et al., in press; Long et al., 2000; Long et al., in press-a). Together, results from these studies indicate that home characteristics, such as ventilation, are the primary determinant of the relationship among personal, indoor, and outdoor particle levels.

A key finding of Sarnat et al is that while ambient PM2.5 concentrations are good surrogates for personal exposure to PM2.5 of ambient origin, ambient concentrations of gaseous air pollutants are not good surrogates of personal exposures to those gases. Rather, they are much better surrogates of personal exposure to PM2.5 of ambient origin. This indicates that reported associations of ambient gases with health outcomes in time series studies may need to be interpreted as effects of particles.

Project Ib: Quantifying Exposure Error and its Effect on Epidemiological Studies

The main objective of this project is to quantify exposure error and to investigate its effect on the observed associations between exposure and health outcome. As mentioned above, the preliminary findings of Project Ia suggest that home characteristics, particularly home ventilation, are the primary determinant of the fraction of outdoor particles that penetrate indoor

environments and thus are an important determinant of personal exposures to particles of outdoor origin as well. Through its impact on exposures to particles of outdoor origin, it is possible that home ventilation may also affect the association between outdoor particle concentrations and health risk. To test this hypothesis, we used data from 14 cities located across the US to examine the relationship between air conditioning prevalence and the coefficient for the relationship between ambient PM_{10} concentrations and cause-specific hospital admissions (Janssen et al, submitted). In addition, we examined whether observed variability in the risk coefficients was specifically related to PM_{10} emissions from mobile, combustion, and other sources. Results from this study indicate that air conditioning use explains a substantial amount of the variability in the risk coefficients from the different cities. Furthermore, PM10 emissions from mobile and diesel sources were also found to be important determinants of the variability in the risk coefficients, particularly for CVD-related hospital admissions.

In the next year, we will continue to investigate factors that affect relationships between personal exposures and outdoor concentrations and will use these data to examine their impact on epidemiological study results and to develop more refined exposure metrics for epidemiological studies.

Project Ic: Differentiating Health Effects of Particles from Outdoor and Indoor Sources

The main objective of this project is to investigate the joint and individual effects of outdoor and indoor particles on heart rate and heart rate variability. We have completed data collection for two field studies conducted in Atlanta and Steubenville, both of which have been co-sponsored by the Center. For the Atlanta study, multi-pollutant exposures and cardiovascular health status were measured repeatedly for two cohorts: individuals with COPD and recent MIs. For the Steubenville study, multi-pollutant exposures and cardiovascular health status were measured for elderly individuals living in government-subsidized housing complexes. The same health protocol was used for each of these studies, with data on heart rate, HRV, blood pressure, oxygen saturation, and daily symptoms obtained for each participant on at least seven days. Twenty-four-hour indoor, outdoor, and personal measurements of particles, ozone, carbon monoxide, nitrogen dioxide were also made on each of the monitoring days. Laboratory and data analysis from the Atlanta study is currently underway, with some results expected to be presented at the 2001 ISEE conference in Germany this September. Laboratory analysis of the Steubenville data is currently on-going, with data analysis expected to start this coming summer. Results from both studies will be reported within the next couple of years.

We have also examined the toxic effects of indoor and outdoor particles using in vitro bioassays. Bioassays were performed using rat alveolar macrophages for 14 paired indoor and outdoor $PM_{2.5}$ samples collected from nine Boston area homes (Long et al, in press-b). Particle induced pro-inflammatory responses were assessed using tumor necrosis factor (TNF) production in the macrophages. Results from this study indicated that TNF production was significantly higher for indoor as compared to outdoor particles, both before and after normalization for endotoxin concentrations.

THEME II: IDENTIFYING POPULATIONS SUSCEPTIBLE TO THE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Project IIa: Examining Conditions in the Elderly which Predispose Towards an Acute Adverse Effects of Particulate Exposures

This project will test the hypothesis that patients with pre-existing respiratory, cardiovascular, or diabetic conditions have an enhanced mortality response to particle exposures. In addition, it will separately assess the effects of gaseous co-pollutants as alternative predictors of mortality and the degree to which they modify response to particulate matter. As part of this we have reported that socio-economic factors were not modifiers of the risk of PM associated mortality (Zanobetti and Schwartz 2000) although there was some increased risk in females. The same pattern held true for hospital admissions for heart and lung disease (Zanobetti, Schwartz, and Dockery 2000). In contrast we found (Zanobetti, Schwartz and Gold, 2000) that respiratory illness modified the risk of cardiovascular hospital admissions associated with PM, and that heart failure modified the risk of PM associated COPD admissions.

More recently we have examined the association of diabetes as an effect modifier for cardiovascular admissions (Zanobetti and Schwartz, in review). We will present the results of these analyses at the ISEE meeting this fall. We intend to proceed to the next step, which will involve mortality followups of subjects whose potentially predisposing conditions were identified use hospital admissions data. These analyses will use the case-crossover approach. We have recently completed a methodological paper examining the potentials for bias and confounding in that approach, and identifying methods for dealing with those problems. That paper (Bateson and Schwartz, in review) is currently in review, and will form the basis for our analyses next year.

Mixed models represent an important tool for determining whether persons with certain characteristics are more susceptible to the effects of airborne particles. However, classic mixed regression programs are linear models, whereas we know that season and weather effects on health are often nonlinear. These have often been addressed using nonparametric smoothing. To further our ability to assess sensitivity while maintaining good covariate control, we have developed an additive mixed model, which combines the attributes of both approaches Coull et al, 2000).

Project IIb: Assessing Life-Shortening Associated with Exposure to Particulate Matter

This main objective of this project is to examine whether particles advance mortality by a few days (harvesting) or have a more profound impact on particle on public health. During the past two years we have published several papers on harvesting. The first two used a smoothing approach to examine the association of PM over time with daily deaths in Boston (Schwartz 2000) and Chicago (Schwartz 2001). Hospital admissions were also examined in the second paper. The main conclusions of our analyses is that particle effects on mortality and morbidity become stronger as average time increases. We then developed a new methodology, using

smoothed distributed lag models, and applied it to data on air pollution and daily deaths in Milan, Italy (Zanobetti et al 2000). This paper confirmed that far from reduced effects, "harvesting resistent" estimates provide estimated effect sizes that are twice as great. Currently, we are extending the long distributed lag approach to examining the harvesting effect in 10 cities in Europe. This paper (Zanobetti et al, in review) is currently in review, and results will be presented this fall at the ISEE meeting.

In a related matter, we have also clarified that control for influenza and other respiratory epidemics does not change the effect size estimates for PM effects on daily deaths (Braga et al, 2000).

Another key issue in assessing the life–shortening effects of PM exposure is the question of dose–response. If there are thresholds for the effects of particles on deaths or hospital admissions then estimates of the public health effect will be overstated. To examine this issue we first developed a new methodology that allows the combination of smoothed dose–response curves from multiple locations. We demonstrated its effectiveness using simulation studies, and applied it to an analysis of PM10 and daily deaths in 10 US cities. There was no deviation from linearity down to the lowest exposure concentrations observed (Schwartz and Zanobetti, 2000). We then extended the methodology to incorporate heterogeneity in response across cities, developing a smoothed estimate that allowed the heterogeneity to vary by exposure level. This new methodology was then applied to 8 cities in Spain, representing the first assessment of dose–response in Europe, where diesel particles are a substantially larger fraction of the total particle mix (Schwartz et al, in press). In addition, we extended the methodology to two pollutant models, and also examined the sensitivity of the shape of the dose–response curve to the way season and weather was controlled. We found a significant linear association between daily deaths and black smoke. The association was little changed by variations in control for weather, season, or SO2. In contrast, for SO2, the association was implausible (inverted U shape) and disappeared with control for black smoke.We have subsequently further expanded the methodology to include random slopes, which allow assessment of predictors of heterogeneity in nonlinear dose–response curves, using hierarchical models. We have applied this to examining the dose-response between PM10 and hospital admissions for heart and lung disease. A manuscript is in preparation.

Finally, we have made important progress in assessing the effect of confounding by co-pollutants on the relation between particles and morbidity and mortality. We have developed a new approach to assessing confounding in a hierarchical model, and applied it to examining the association between PM10 and daily deaths (Schwartz, 2000). This approach showed that associations were not confounded by gaseous air pollutants. The methodology was then applied to a year and season specific analysis of data from Philadelphia to confirm that the association was with particles, and not SO2, and to demonstrate that it was predominantly associated with the finer particles (Schwartz 2000).

Project IIc: Investigating Chronic Effects of Exposure to Particulate Matter

As part of this project we will follow up the Six Cities Study cohort up to twenty four years in an effort to assess the cumulative effect of long-term exposures on the incidence of lung cancer, nonmalignant respiratory disease, cardiovascular disease, and cause-specific mortality. Also another objective of this project is to estimate the years lost associated with particulate exposure.

Vital status was determined for the 8111 participants in the Harvard Six Cities adult cohort for an additional nine years of follow-up (1990-1998). We identified 1430 additional deaths brining the total to 2737 deaths. Survival analyses of all-cause mortality shows that life expectancy continues to be reduced in the more polluted cities, with the relative ranking of the survival the same as in the original published analyses. We are also investigating how the risk varies with the baseline age of the members of the cohort. In the coming year we will construct an air pollution timeline for each city, analyze cause-specific mortality, and estimate the net years of life lost attributable to particulate air pollution.

Project IId: Determining the effects of Particle Characteristics on Respiratory Health of Children

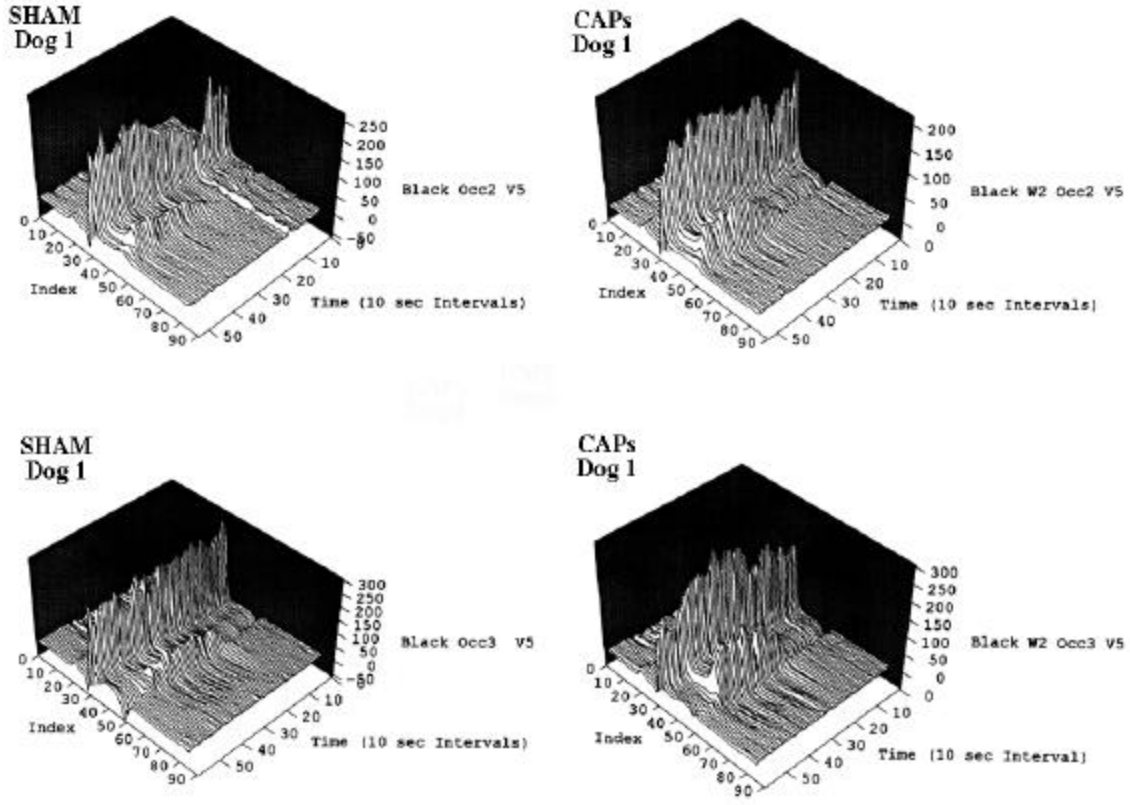
The main objective of this project is to examine the effects of particle composition on the respiratory health of children using particle samples collected as part of the Harvard Twenty-Four Cities Study. Due to time constrains and research staff availability this project has not been initiated yet. We hope to select and analyze the samples this coming year and do the statistical analysis in the next year.

THEME III: BIOLOGICAL MECHANISMS AND DOSIMETRY

Project IIIa: Differentiating the Roles of Particle Size, Particle Composition and Gaseous Co-Pollutants on Cardiac Ischemia

The main aim of this study is to investigate the effects of concomitant gaseous co-pollutants, particle size, and particle composition using a dog cardiac ischemia model and our recently developed particle concentrator technologies. We have developed and tested simplified variations in the protocol of the dog ischemia model in order to establish a response pattern that could be used in studies of pharmacologic interventions to define mechanistic effects. In the general ischemia model protocol, a 5 min conditioning occlusion with a 20 min recovery period is followed by a second and sometimes third 5 min occlusion. Previously, we had done the conditioning and one occlusion prior to an exposure of concentrated air particles (CAPs), and a third occlusion after the exposure. These occlusions took place on the third day of a 3-day, 6 hrs/day CAPs or sham exposure protocol with cross-over the following week. Using 3-dimensional electrocardiograms, a positive response pattern in the same dog under CAPs conditions compared to sham is illustrated. In this example, the 2nd occlusion in the CAPs dog has a higher ST segment and higher T wave than the same dog in her second occlusion as sham.

The 3rd occlusion in the CAPs dog has an earlier onset, higher ST segments, and higher T-waves than either the 2nd CAPs or either sham occlusions.



This suggests that there may be carry-over of effect from the previous day's CAPs exposure as well as augmentation of the effect on the third day. However, this pattern was not consistent from week to week. As in many other of our laboratory experiments with CAPs, it appeared that composition may be the determining factor in this variability, but this protocol was not designed to carry out large numbers of experiments to pursue this issue, nor was it capable of testing the hypothesis of carry-over of effects from day to day.

A simplified version of the dog ischemia model protocol was therefore developed. This also involves two dogs studied at the same time. The first day, both dogs are sham exposed and have one conditioning and one test occlusion after exposure. The second day, one dog is exposed to CAPs and her chamber-mate is sham exposed with conditioning and test occlusions following exposure. The dogs cross-over for the third day's exposure so that the dog who was sham exposed the day before, now receives CAPs, and occlusions are done after exposure. The fouth day both dogs are sham exposed with occlusions again following exposure. Outcomes assessed include time and magnitude of ST segment elevation, T-wave morphology, heart rate, and heart rate variability. Preliminary analyses indicate: 1) that there does appear to be a carry-over of effect after the first day of CAPs exposure in the ST-segment changes; 2) this carry-over does not extend to the second day post-exposure; 3) there is day to day variability in the magnitude of the responses; and 4) this protocol is more suited to assess large numbers of exposure days and

hence useful to assess compositional variability as a cause of the magnitude of change in response. Twenty CAPs exposure days have been completed using 5 different dogs. Compositional analysis of the exposure is underway as is detailed electrocardiogram analyses. These will be completed within the next few months so that it can be determined if this protocol can be used for interventional mechanistic studies.

In addition, we have developed a rat model of acute myocardial infarction in order to study the effects of CAPs on ischemia induced arrhythmias. In these studies, a myocardial infarction is surgically induced in rats. On the following day, the rats are given either a particle or sham exposure and the electrocardiogram is continuously monitored before, during, and after exposure. Studies using this approach have used fly ash, carbon black, and CAPs to assess arrhythmias. Both fly ash and CAPs exposures significantly increase the number of premature ventricular contractions (PVCs) in animals that have PVCs in their baseline. Sham and carbon black exposures do not increase PVCs. This appears to be a sensitive model of cardiac effects of CAPs and we are now using this approach to study the influence of gaseous co-pollutants on the CAPs effect. Studies are beginning with carbon monoxide and will be followed by ozone. This rat model also appears to be useful for interventional pharmacologic experiments to determine the pathophysiologic mechanism(s) triggering the observed arrhythmias. These studies will also begin in the coming year.

Project IIIb: Assessing Deposition of Ambient Particles in the Lung

The main objective of this project is to use *in situ continuous* respiratory and total deposition measurements to develop a new regional deposition.

To date, we have conducted a series of exposure experiments to test the hypothesis that the lung deposition of ambient particles (i.e., CAPs) can not be adequately described based on findings with conventionally used 'test particles' such as iron oxide particles because of the complex physicochemical properties of CAPs. In the course of eight experiments performed so far, dogs were exposed to CAPs and control particles (Fe2O3; mean diameter of 0.7um) and the total deposition of these particles was computed and compared over a wide range of particle size (40nm-3um). The initial results showed that, 1) changes in relative humidity along the airways influenced CAPs characteristics and consequently their behavior in the respiratory tract and 2) the total deposition of CAPs was substantially higher than that of control particles. These results suggest that the hygroscopic properties of CAPs may be important in determining deposition, and that the estimation based on nonhygroscopic control particles could be misleading by substantially underestimating the particle deposition for a given exposure. In the coming grant year, we plan to study dosimetry of CAPs in human subjects.

Project IIIc: Relating Changes in Blood Viscosity, Other Clotting Parameters, Heart Rate and Heart Rate Variability to Particulate and Criteria Gas Exposures

The main objective of this Project is to investigate associations of selected inflammatory and blood clotting parameters in free living humans with particle and criteria gas exposures. This project is in collaboration with the Boston Veterans Hospital who is currently conducting the Normative Aging Study (NAS). During the first two years the VA Hospital has been collecting

data which will be turned next year to the Harvard School of Public Health for the statistical analysis.

REFERENCES

Braga AL, Zanobetti A, Schwartz J. Do respiratory epidemics confound the association between air pollution and daily deaths? Eur Respir J 2000;16(4):723-8.

Coull BA, Schwartz J, and Wand MP. Respiratory Health and Air Pollution: Additive Mixed Model Analyses. Biostatistics, in press.

Janssen, N.A.H., Schwartz, J., Zanobetti, A., Suh, H.H. (Submitted for publication). "Air conditioning and combustion related particles as modifiers of the effect of PM10 on hospital admissions for heart and lung disease".

Long, C.M., Suh, H.H., Koutrakis, P. (2000) "Characterization of Sources of Indoor Particle Sources using Continuous Mass and Size Monitors." Journal of Air and Waste Management Association, 50:1236-1251.

Long, C. M., Suh, H. H., Catalano, P. J., Koutrakis, P. (In press-a) "Using Time- and Size-Resolved Particulate Data to Quantify Penetration and Deposition Behavior". Environmental Science & Technology.

Long, C. M., Suh, H. H., Kobzik, L., Catalano, P. J., Ning, Y. Y., Koutrakis, P. (In press-b) "A Pilot Investigation of the Relative Toxicity of Indoor and Outdoor Fine Particles: In-Vitro Effects of Endotoxin and Other Particulate Properties". Environmental Health Perspectives.

Saldiva, H. N., Clarke, R. W., Stearns, R., Lawrence, J., Koutrakis, P., Suh, H., Tsuda, A., Coull, B., Godleski, J. G. Acute Pulmonary Inflammation Induced by Concentrated Ambient Particles and its Relationship to Particle Composition. Manuscript in preparation.

Sarnat, J. A., Koutrakis, P. Suh, H. H. (2000) "Assessing the Relationship between Personal Particulate and Gaseous Exposures of Senior Citizens Living in Baltimore, MD." Journal of the Air and Waste Management Association, 50:1184-1198.

Sarnat, J. A., Schwartz, J., Catalano, P. J., Suh, H. H. (In press) "Confounder or Surrogate: The Role of Gaseous Pollutants in Particulate Matter Epidemiology." Environmental Health Perspectives.

Schwartz J. Harvesting and long-term exposure effects in the relationship between air pollution and mortality. Am J Epidemiology 2000;151:440-448.

Schwartz J. Is There Harvesting in the Association of Airborne Particles with Daily Deaths and Hospital Admissions? Epidemiol 2001;12:55-61.

Schwartz J and Zanobetti A. Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 2000;11(6):666-672

Schwartz J, Ballester F, Saez M, Pérez-Hoyos S, Bellido J, Cambra K, Arribas F, Cañada A, Pérez-Boillos MJ, and Jordi Sunyer J. The ConcentrationResponse Relation between Air Pollution and Daily Deaths. Environmental Health Perspectives, In press.

Schwartz J. Assessing Confounding, Effect Modification, and Thresholds in the Association between Ambient Particles and Daily Deaths. Environ Health Perspect 2000;108:563-568.

Schwartz J. Daily deaths are associated with combustion particles rather than SO2 in Philadelphia. Occup Environ Med 2000; 57:692-697.

Zanobetti A and Schwartz J. Race, gender and social status as modifiers of the effects of PM_{10} on mortality. J Occup Environ Med 2000;42:469-474.

Zanobetti A, Schwartz J, Dockery DW. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 2000;108:1071-1077.

Zanobetti A, Schwartz J, Gold DR. Are the sensitive subgroups for the health effects of airborne particles? Environ Health Perspect 2000;108:841-845.

Zanobetti A, Wand MP, Schwartz J, and Ryan L. Generalized Additive Distributed Lag Models: Quantifying Mortality Displacement. Biostatistics 2000;1:279-292.